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Effects of gentamicin monotherapy for the initial treatment of community-onset complicated non-obstructive acute pyelonephritis due to Enterobacteriaceae in elderly and non-elderly women

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Abstract

Aminoglycosides may serve as fluoroquinolone-sparing or cephalosporin-sparing agents if the clinical effectiveness of aminoglycoside monotherapy is demonstrated. The purposes of this study were to investigate the clinical efficacy of gentamicin as an initial empirical antimicrobial agent and to evaluate the effects of gentamicin resistance on clinical outcomes in women with complicated non-obstructive acute pyelonephritis (APN). Medical records of 1066 women with a diagnosis of APN were reviewed retrospectively. We enrolled 275 women with community-onset complicated non-obstructive APN due to Enterobacteriaceae who received gentamicin as their initial antibiotic. Of these 275 patients, 43 had gentamicin-resistant (GM-R) Enterobacteriaceae APN, and 232 had gentamicin-susceptible (GM-S) Enterobacteriaceae APN. The early clinical success rates were 67.4% (29/43) versus 89.7% (208/232) at 72 h in the GM-R versus the GM-S groups (p 0.001). The overall clinical cure rate was 100% (43/43) and 98.7% (229/232) in the GM-R and GM-S groups, respectively. The duration of hospital stay was significantly longer in the elderly, although there were no significant differences in the rates of early clinical success, final clinical cure, mortality, and time to fever clearance between the elderly and non-elderly groups. Resistance of Enterobacteriaceae to gentamicin, haematuria and serum C-reactive protein level ≥20 mg/dL were independently associated with early clinical failure. Gentamicin can be an effective initial antibiotic option for empirical therapy in women with community-onset complicated APN who do not need urological interventional procedures. The use of gentamicin may contribute to a reduction of fluoroquinolone or broad-spectrum cephalosporin use in the treatment of complicated APN.

Keywords: Acute pyelonephritis, diabetes, elderly, gentamicin
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Introduction

Patients with complicated acute pyelonephritis (APN) are a highly heterogeneous group, with comorbidities such as diabetes mellitus, nephrolithiasis, renal impairment, immunocompromised status, or other functional and anatomical abnormalities of the urinary tract that require urological interventions, such as surgery, percutaneous drainage, catheterization and dialysis [1–3].

Most guidelines for APN have focused on premenopausal women with uncomplicated APN, most likely as a result of the homogeneity of the patient population and the larger research databases available [4,5]. Elderly or diabetic women with community-onset APN in whom no urological interventions are necessary can be treated effectively with antimicrobial agents alone, similar to patients with uncomplicated APN [6–8].

Gentamicin is an antibiotic option for the initial empirical therapy of community-acquired uncomplicated APN [9–11]. However, there have been few clinical studies focusing on the use of gentamicin as an initial empiric antibiotic therapy for

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complicated APN. In this study, gentamicin was administered as an initial empirical antimicrobial agent in hospitalized APN patients with complicating factors, in whom no urological intervention was indicated. We analysed the clinical efficacy of gentamicin monotherapy.

Materials and Methods

Setting and study design

This study was retrospectively performed at the Catholic University St Vincent's Hospital, a 791-bed teaching hospital in South Korea between March 2000 and February 2011. The Institutional Review Board (IRB) of the Catholic University St Vincent's Hospital reviewed and approved all protocols in this study. The IRB waived the requirement for written, informed consent from each patient in this study. All the data collected for this study were kept confidential.

Patient population

We included all women with community-onset complicated APN by Enterobacteriaceae. APN was defined by a fever of ≥38.0°C and the presence of pyuria on microscopic examination of the urine (>5–10 leucocytes/high-power field) and positive urine culture (≥10^5 CFU/mL for clean voided urine, and 10^4 CFU/mL for catheterized urine) [9,12,13]. APN was considered 'complicated' in the presence of any systemic underlying disorder (diabetes mellitus, renal disease, kidney transplantation, connective tissue disorder, cerebrovascular disease, malignancy, pregnancy, immunosuppression), and/or urinary tract abnormalities (renal stone, kidney malformation, urological malignancy, polycystic kidney disease, vesicoureteral reflux, neurogenic bladder), or age greater than 65 years [2,14]. Patients were excluded if they were diagnosed with APN more than 48 h after admission or if they had a urinary catheter-related infection or a complicated obstructive APN requiring a urological interventional procedure such as surgery, percutaneous drainage, or catheterization for the purpose of relieving the obstruction. Patients who did not have radiological data consisting of computerized tomography (CT) were also excluded.

Clinical data collection

Clinical data on age, medical history, comorbid conditions, urinary tract conditions, urinary symptoms, relevant physical findings, laboratory results, the duration of intravenous and oral antibiotic administration, microbiological data, days to defervescence, hospitalization days, mortality and adverse drug events were collected and analysed by chart review.

Subjective symptoms of ototoxicity regarding dizziness, vertigo, hearing impairment, medical records of ototoxicity and laboratory evidences of acute kidney injury after gentamicin treatment were collected. Radiological CT data were available for all patients because abdominal CT scan was performed as the diagnostic approach for complicated APN to identify the presence of anatomical abnormalities or obstructive lesions.

Clinical outcome measures and definition

Treatment outcomes were assessed in terms of early clinical success after 72 h of treatment, final clinical outcome (clinical cure or failure), hospitalization days, and time to defervescence. Early clinical success at 72 h was defined as resolution of fever with improvement of urinary tract symptoms or signs within 72 h after the start of gentamicin monotherapy. Those patients who did not meet the criteria of early clinical success were regarded as early clinical failures. Clinical cure was defined as the absence of symptoms or signs at completion of therapy and/or at a 4-day to 10-day follow up, when available [15]. Clinical failure was defined as the recurrence of urinary tract symptoms and/or signs at completion of therapy, or at a 4-day to 10-day follow up. Resolution of fever was defined as an afebrile state where the body temperature (tympanic) remained at 37.0°C or below for 24 h or longer [9]. Time to defervescence was defined as the time from the start of gentamicin monotherapy to an afebrile state. The tympanic temperatures of each patient were measured every 6 h during hospitalization.

Acute kidney injury was defined as an absolute serum creatinine increase >3 mg/dL or a relative increase in serum creatinine >50%, in accordance with the Acute Kidney Injury Network criteria [16]. Haematuria was defined as ≥5–9 red blood cells/high-power field on microscopic examination of urine.

Microbiological data

Urine specimens were plated using a 0.001-mL inoculating loop for quantification and incubated. Whole blood samples taken from women with complicated APN were also incubated. Aetiological agents were determined by ≥10^5 CFU/mL organisms identified on urine culture, or isolation of urinary pathogens from blood cultures [17,18]. Species identification and susceptibility to antimicrobial agents were determined by means of either a semiautomated system (Microscan; DADE Behring, West Sacramento, CA, USA) or disc diffusion susceptibility tests according to the criteria of the CLSI [19]. The MIC cutoff for gentamicin resistance was ≥8 mg/L.

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Statistical methods

Results are expressed as the mean ± standard deviation, or number (percentage). Comparisons between categorical variables were assessed by using a Fisher's exact test or the Pearson chi-square test. Continuous variables were analysed by the independent *t* test or the Mann–Whitney *U* test. Logistic regression analysis was performed to evaluate the effects of independent variables on clinical outcome. A multivariate analysis was performed using logistic regression to evaluate the effects of independent variables on early clinical failure in the patients with complicated non-obstructive APN who were treated with gentamicin monotherapy. Tests with a probability of <0.05 were considered statistically significant. SPSS version 21.0 for Windows (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Demographic and clinical characteristics

A total of 1066 patients with a diagnosis of community-onset APN were identified. Of the 649 patients treated by gentamicin monotherapy, 629 had positive urine and/or blood culture for Enterobacteriaceae. Among them, 298 women had complicated APN. Of these, 23 were excluded because of urological abnormalities that required urological interventions or the absence of radiological data. Finally, 275 cases of community-onset complicated non-obstructive APN were enrolled and analysed (Fig. 1).

Of the 275 women, 130 women were non-elderly with complicating factors and 145 women were elderly with or without complicating factors. Although the frequencies of hypertension, cerebrovascular diseases and congestive heart failure were significantly higher in the elderly group, the frequencies of diabetes mellitus and urolithiasis were significantly higher in the non-elderly group. There were no significant differences in initial body temperature, leucocyte counts, C-reactive protein (CRP) levels, the frequencies of lower urinary tract infection (UTI) symptoms, flank pain, costovertebral angle tenderness, haematuria, bacteraemia, and uropathogen resistance to gentamicin between the elderly and non-elderly groups. There were no significant differences in the rates of final clinical cure, mortality, early clinical success, and time to fever clearance between these groups. Median duration of hospital stay in the elderly and non-elderly groups were 10 (8–13) and 9 (7–11) days, respectively, significantly longer in the elderly group (p 0.023) (Table 1).

When the elderly group was stratified into two groups according to the presence of other complicating factors, the elderly group with other complicating factors had higher CRP levels and received a lower dose of gentamicin; however, there were no significant differences in clinical outcomes, such as final clinical cure, early clinical success, mortality and duration of hospital stay (Table 2).

Microbiological data

In the 275 cases, *Escherichia coli* was the most common pathogen (258 patients; 93.8%) and non-*E. coli* Enterobacteriaceae were isolated from 17 patients (6.2%). Non-*E. coli* Enterobacteriaceae comprised eight *Klebsiella pneumoniae*, two *Citrobacter freundii*, two *Citrobacter koseri*, two *Enterobacter aerogenes*, two *Proteus mirabilis* and one *Enterobacter cloacae*. The antimicrobial susceptibility profiles of the 258 *E. coli* isolates and the 17 non-*E. coli* isolates are shown in Table 3.

Clinical outcomes according to the presence of gentamicin-resistant Enterobacteriaceae

Of 275 women with complicated APN, 43 patients had gentamicin-resistant (GM-R) Enterobacteriaceae, and 232 patients had gentamicin-sensitive (GM-S) Enterobacteriaceae. Fifteen (34.9%) of 43 patients in the GM-R group were switched to alternative intravenous therapy. The early clinical success rates were 32.6% (14/43) versus 62.1% (144/232) at 48 h, 67.4% (29/43) versus 89.7% (208/232) at 72 h, and 81.4% (35/43) versus 95.7% (222/232) at 96 h in the GM-R versus GM-S groups ($p \leq 0.001$). Median time to defervescence was 60 h (interquartile range (IQR), 40–78) and 40 h (IQR, 30–56) in the GM-R and GM-S groups, respectively ($p < 0.001$) (Fig. S1). Overall clinical cure rates were 100% (43/43) and 98.7% (229/232) in the GM-R and GM-S groups, respectively ($p > 0.999$). The median number of hospitalization days in the GM-R and GM-S groups was 9 (IQR, 7–12) and 10 (IQR, 8–12), respectively (p 0.677) (Table 4). No complications, such as death, progression to septic shock, or renal and perirenal abscess, occurred in either the GM-R or GM-S groups. Microbiological outcomes were available in only 50 of 275 women at a 4–10-day follow up after completion of antimicrobial therapy. Microbiological cure rates were 92.1% (35/38) and 91.7% (11/12) in the GM-R and GM-S groups, respectively, ($p > 0.999$) at a 4–10-day follow up.

Factors related to early clinical failure in women with community-onset non-obstructive APN

Among 275 cases, 237 cases were placed in the early clinical success group (at 72 h), and 38 in the early clinical failure group. There were no significant differences in age, proportion of elderly patients, initial body temperature, initial leucocyte counts, the frequencies of lower UTI symptoms, flank pain or costovertebral angle tenderness. However, the frequencies of

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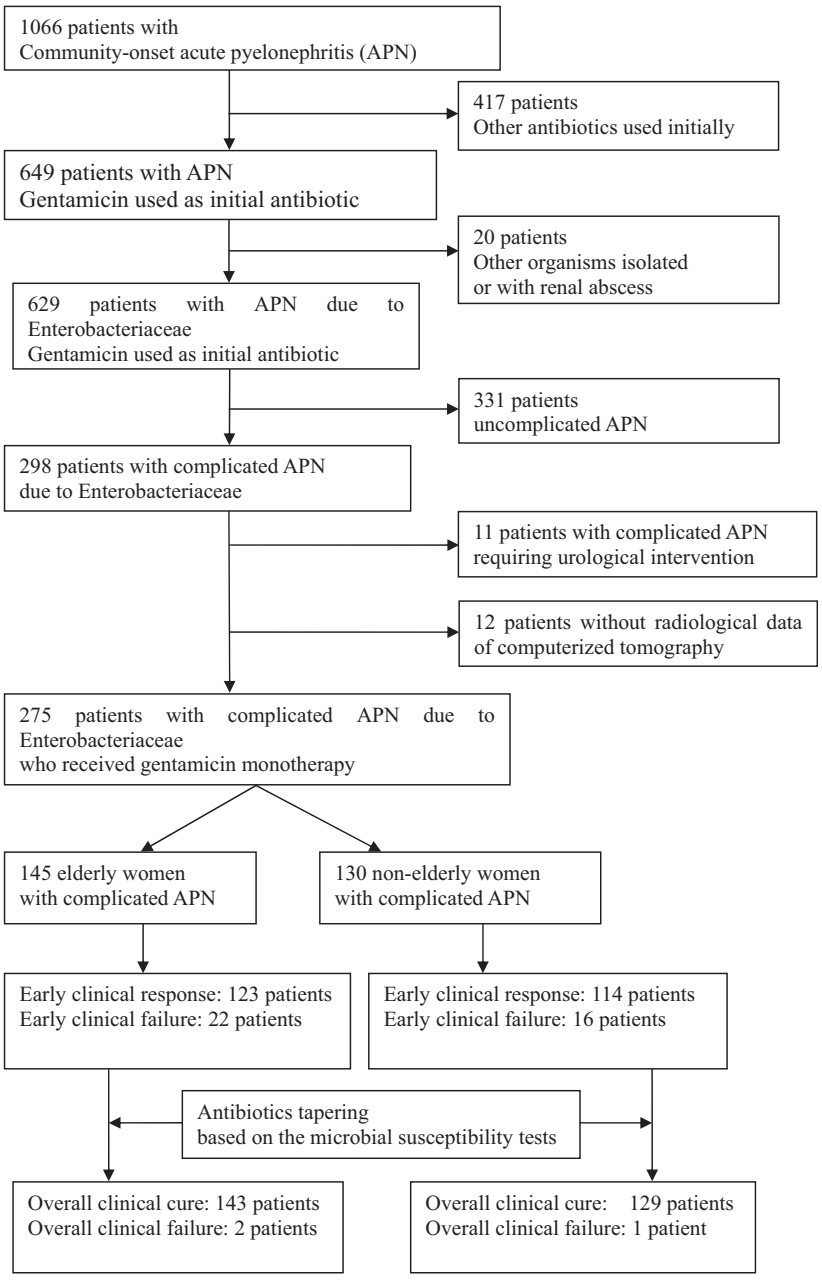

FIG. 1. Subjects enrolment and retrospective analysis (total acute pyelonephritis).

previous history of UTI (24.1% versus 7.9%; p 0.032), antibiotic usage within 1 year (24.9% versus 2.6%; p 0.001), and previous history of admission within 1 year (26.2% versus 2.6%; p 0.001) were significantly higher in the early clinical success group. Initial CRP levels (18.0 ± 8.2 versus 12.0 ± 7.4; p <0.001) were significantly higher, and the frequencies of haematuria (71.1% versus 51.1%; p 0.022) and bacteraemia (42.1% versus 19.0%; p 0.001) were also significantly higher in the early clinical failure group. Furthermore, Enterobacteriaceae susceptibility to gentamicin was significantly lower in the early clinical failure group (63.2% versus 87.8%; p <0.001). There were no significant differences in the prevalence of diabetes, hypertension, cerebrovascular diseases, congestive heart failure, chronic liver diseases, chronic lung diseases, malignancy and menopause between the early clinical failure and clinical response groups. Although median duration of hospital stay (11 (9.75–14) versus 9 (7–12) days; p 0.012) was longer in the early clinical failure group, there were no significant differences in the rates of overall clinical cure and mortality. On mulivariate analysis, resistance to gentamicin, haematuria, and serum CRP level ≥20 mg/dL were significantly associated with early clinical failure (p <0.001, p 0.012, and p 0.026) (Table S1).

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TABLE 1. Demographic and clinical characteristics of elderly and non-elderly women with community-onset complicated non-obstructive acute pyelonephritis due to Enterobacteriaceae

Characteristics	Elderly	Non-elderly	p-Value[a]
Number of patients	145	130	
Age (median, IQ–3Q) (years)	71, 68–76	47, 36–54	
Past history			
Antibiotic use within 1 year	22 (15.2)	36 (27.7)	0.011
Previous urinary tract infection	17 (11.7)	43 (33.1)	<0.001
Admission within 1 year	23 (15.9)	40 (30.8)	0.003
Comorbid conditions			
Diabetes mellitus	49 (33.8)	90 (69.2)	<0.001
Hypertension	60 (41.4)	22 (16.9)	<0.001
Cerebrovascular diseases	11 (7.6)	2 (1.5)	0.022
Congestive heart failure	10 (6.9)	2 (1.5)	0.038
Chronic liver diseases	10 (6.9)	4 (3.1)	0.178
Chronic lung diseases	4 (2.8)	3 (2.3)	>0.999
Malignancy	7 (4.8)	1 (0.8)	0.07
Menopause	145 (100)	57 (43.8)	
Urinary tract conditions			
Urolithiasis	7 (4.8)	34 (26.2)	<0.001
Vesicoureteral reflux	2 (1.4)	7 (5.4)	0.089
Clinical and laboratory features			
Initial body temperature (°C)	38.7 ± 0.7	38.6 ± 0.6	0.536[b]
Lower urinary tract infection symptoms	90 (62.1)	84 (64.6)	0.662
Flank pain	120 (82.8)	117 (90.0)	0.082
Costovertebral angle tenderness	121 (83.4)	116 (89.2)	0.165
Hematuria (≥5–9 red blood cells/HPF)	84 (57.9)	64 (49.2)	0.149
White blood cell counts (cells/mm^3)	11 925 ± 4560	11 212 ± 4568	0.197[b]
White blood cells ≥20 000/mm^3 of blood	8 (5.5)	5 (3.8)	0.514
C-reactive protein (mg/dL)	12.9 ± 7.2	12.8 ± 8.3	0.941[b]
C-reactive protein ≥20 mg/dL	23 (15.9)	23 (17.7)	0.685
Bacteremia	38 (26.2)	23 (17.7)	0.09
Uropathogen resistant to gentamicin	21 (14.5)	22 (16.9)	0.578
Clinical outcomes			
Final clinical cure	143 (98.6)	129 (99.2)	>0.999
Mortality	0	0	
Early clinical success (at 72 h)	123 (84.8)	114 (87.7)	0.492
Time to fever clearance (hours), median (IQ–3Q)	41.5 (30–60)	40 (32–62)	0.983[b]
Hospitalization period (days), median	10 (8–13)	9 (7–11)	0.023[b]
Adverse drug events			
Acute kidney injury	1 (0.7)	2 (1.5)	0.604
Ototoxicity	0	0	
Stop due to other adverse effects	1 (0.7)	1 (0.8)	>0.999

Data are shown as numbers of patients (% of total) or mean ± standard deviation/median as appropriate.
[a]Chi-square test or Fisher's exact test.
[b]Mann–Whitney *U* test.

All of 275 patients had follow up at completion of therapy. However, only 127 (46.2%) of 275 patients had follow up at 4–10 days after the end of antimicrobial therapy. The clinical success rates were 99.6% (236/237) versus 100% (38/38) at completion of therapy in the early clinical success versus the early clinical failure groups (p 0.688). The clinical success rates were 97.2% (105/108) versus 100% (19/19) at 4–10 days after the end of antimicrobial therapy in the early clinical success versus the early clinical failure groups. Microbiological cure rates were 93.6% (44/47) and 66.7% (2/3) in the early clinical success and the early clinical failure groups, respectively, (p 0.226) at 4- to 10-day follow up after completion of antimicrobial therapy.

Discussion

The data in this study showed that the final clinical cure rate and microbiological cure rate were 98.9% and 92.0%, respectively, in the gentamicin-treated women with complicated APN. In addition, the early clinical success rates were 86.2% and 93.5%, respectively, at 72 and 96 h after the start of gentamicin monotherapy. In particular, 36 of 43 patients with complicated APN due to GM-R Enterobacteriaceae had defervescence before or without switching to alternative intravenous antibiotics.

The overall clinical cure rate, number of hospitalization days and mortality rate were not significantly different between the GM-R and GM-S groups in this study, even though APN patients in the GM-R group had a lower early clinical response rate than those in the GM-S group.

Although the duration of hospital stay was significantly longer in the elderly, there were no significant differences in the rates of early clinical success, final clinical cure, mortality and time to fever clearance between the elderly and non-elderly women. These results suggest that gentamicin may be an antibiotic option in elderly women with APN. The early clinical success rates at 72 and 96 h (86.2% and 93.5%) were higher than those of women with uncomplicated APN due to *E. coli* in our previous study, in which the early clinical success rates at 72 and 96 h were 77.0% and 90.9% [9].

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TABLE 2. Clinical characteristics and outcomes in elderly women with community-onset complicated non-obstructive acute pyelonephritis by the presence of other complicating factors

Characteristics	Elderly with other complicating factors	Elderly without other complicating factors	p-Value[a]
Number of patients	55	90	
Age (median, 1Q–3Q) (years)	70, 67–73	73, 68–77	<0.001
Past history			
Antibiotic use within 1 year	8 (14.5)	14 (15.6)	0.869
Previous urinary tract infection	8 (14.5)	9 (10.0)	0.409
Admission within 1 year	8 (14.5)	15 (16.7)	0.734
Complicating factors			
Diabetes mellitus	49 (89.1)	0	<0.001
Urolithiasis	7 (12.7)	0	0.001
Vesicoureteral reflux	2 (3.6)	0	0.142
Clinical and laboratory features			
Initial body temperature (°C)	38.6 ± 0.6	38.8 ± 0.7	0.054[b]
Hematuria (≥5–9 red blood cells/HPF)	31 (56.4)	53 (58.9)	0.765
White blood cell counts (cells/mm^3)	12 749 ± 4872	11 421 ± 4309	0.089[b]
White blood cells ≥20 000/mm^3 of blood	4 (7.3)	4 (4.4)	0.478
C-reactive protein (mg/dL)	14.8 ± 8.3	11.7 ± 6.2	0.018[b]
C-reactive protein ≥20 mg/dL	15 (27.3)	8 (8.9)	0.003
Bacteremia	12 (21.8)	26 (28.9)	0.437
Uropathogen resistant to gentamicin	5 (9.1)	16 (17.8)	0.149
Dose of gentamicin (mg/kg per day)	4.46 ± 0.77	4.79 ± 0.92	0.033[b]
Dosing type of gentamicin	Once-daily dosing	Once-daily dosing	
Duration of gentamicin (days)	6.98 ± 1.41	6.61 ± 1.56	0.151
Clinical outcomes			
Final clinical cure	54 (98.2)	89 (98.9)	>0.999
Mortality	0	0	
Early clinical success (at 72 h)	47 (85.5)	76 (84.4)	0.869
Time to fever clearance (hours), median (1Q–3Q)	42 (30–60)	42.5 (30–63)	0.486[b]
Hospitalization period (days), median (1Q–3Q)	12 (8–14)	10 (8–12)	0.075[b]

Data are shown as numbers of patients (% of total) or mean ± standard deviation/median as appropriate.
[a]Chi-square test or Fisher's exact test.
[b]Mann–Whitney *U* test.

TABLE 3. Antimicrobial susceptibilities of *Escherichia coli* and non-*E. coli* Enterobacteriaceae isolated from women with community-onset complicated non-obstructive acute pyelonephritis

Antibiotics	*E. coli* (*n* = 258)				Non-*E. coli* Enterobacteriaceae (*n* = 17)			
	Resistant (*n*)	Susceptible (*n*)	Total (*n*)	Susceptibility (%)	Resistant (*n*)	Susceptible (*n*)	Total (*n*)	Susceptibility (%)
Amikacin	1	257	258	99.6	0	17	17	100
Gentamicin	43	215	258	83.3	0	17	17	100
Tobramycin	17	73	90	81.1	0	7	7	100
Ampicillin	101	50	151	33.1	6	5	11	45.5
AMOX/CLA	40	68	108	63.0	3	6	9	66.7
Piperacillin	120	77	197	39.1	3	14	17	82.4
TZP	6	249	255	97.6	0	17	17	100
Cephradine	114	140	254	55.1	3	14	17	82.4
Cefuroxme	18	239	257	93.0	1	16	17	94.1
Cetotaxime	7	250	257	97.3	1	16	17	94.1
Ceftriaxone	7	88	95	92.6	1	10	11	90.9
Ceftazidime	6	225	231	97.4	1	13	14	92.9
Cefepime	6	98	104	94.2	0	17	17	100
Imipenem	0	256	256	100	0	17	17	100
Ciprofloxacin	44	214	258	82.9	3	14	17	82.4
SXT	107	151	258	58.5	2	15	17	88.2

AMOX/CLA, amoxicillin/clavulanate; TZP, piperacillin/tazobactam; SXT, trimethoprim-sulfamethoxazole.

Current classification based on the concept of the two main categories, complicated and uncomplicated APN, may cause confusion [20]. In fact, the clinical spectrum of complicated APN ranges from severe cases with complicated APN requiring urological interventional procedures for relieving obstructions, to relatively mild cases that are easily treated with first-line antimicrobial agents. However, there are few well-designed clinical trials examining the treatment of community-onset complicated APN [3].

Aminoglycosides are used less frequently than broad-spectrum cephalosporins or fluoroquinolones and are usually administered in combination with other antibiotics in the treatment of most infectious diseases. However, aminoglycoside monotherapy can be used in the treatment of UTIs, as aminoglycosides achieve a much higher renal tissue concentration than other antibiotics. In recent years there have been few adequate studies concerning the use of gentamicin in the treatment of complicated APN.

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TABLE 4. Clinical outcomes of women with community-onset complicated non-obstructive acute pyelonephritis treated with gentamicin monotherapy as initial empirical antibiotics

Characteristics	Complicated APN due to gentamicin resistant Enterobacteriaceae	Complicated APN due to gentamicin-susceptible Enterobacteriaceae	p-Value[a]
Number of patients	43	232	
Age (median, 1Q–3Q) (years)	56, 38–72	66, 50–72	0.079[b]
Dose of gentamicin (mg/kg per day)	4.79 ± 1.05	4.54 ± 0.90	0.103[b]
Dosing type of gentamicin	Once-daily dosing	Once-daily dosing	
Duration of gentamicin (days)	5.63 ± 1.87	6.87 ± 1.28	<0.001
Number of cases receiving alternative intravenous antibiotics	15 (34.9)	6 (2.6)	<0.001
Alternative intravenous antibiotics (No. of cases)			
Cefuroxime	9	5	<0.001
Amikacin	5	1	<0.001
Cefotaxime	1	0	0.156
Switch to oral antibiotics (No. of cases)			
Amoxicillin	9	36	0.378
Ciprofloxacin	9	66	0.309
First cephalosporin	9	53	0.783
Second cephalosporin	7	35	0.842
Third cephalosporin	3	4	0.079
Trimethoprim-sulfamethoxazole	4	36	0.354
Amixicillin/calvalanate	0	1	>0.999
Duration of oral antimicrobial therapy (days)	6.70 ± 1.93	6.95 ± 1.24	0.417
Duration of total antimicrobial therapy (days)	14.56 ± 2.05	13.98 ± 0.89	0.075
Final clinical cure	43 (100)	229 (98.7)	>0.999
Mortality	0	0	
Time to fever clearance (hours), median (1Q–3Q)	60 (40–78)	40 (30–56)	<0.001
Defervescence			
Within 24 h	3 (7.0)	32 (13.8)	0.319
Within 48 h	14 (32.6)	144 (62.1)	<0.001
Within 72 h	29 (67.4)	208 (89.7)	<0.001
Within 96 h	35 (81.4)	222 (95.7)	<0.001
Within 120 h	36 (83.7)	229 (98.7)	<0.001
Hospitalization period (days), median	9 (7–12)	10 (8–12)	0.677
Adverse drug events			
Acute kidney injury	0	3 (1.4)	>0.999
Ototoxicity	0	0	
Stop due to other adverse effects	0	2 (0.9)	>0.999

Data are shown as numbers of patients (% of total) or mean ± standard deviation/median as appropriate.
[a]Chi-square test or Fisher's exact test.
[b]Mann–Whitney *U* test.

It has been known that ototoxicity and nephrotoxicity are the major toxicities of aminoglycosides, and once-daily aminoglycoside dosing has been used for the purpose of reducing toxicities. Gentamicin ototoxicity may be mainly vestibular, not cochlear, and produce loss of balance. Gentamicin can be vestibulotoxic in any dose, at any serum level [21–24]. However, patients with ototoxicity were not identified, and the rate of observed nephrotoxicity was 1.1% in this study and much lower compared with the reported rates of gentamicin nephrotoxicity from 1.2% up to 55% in previous studies [25].

This study has a few limitations. First, this was a retrospective study. Therefore, the data for the comorbid conditions, past history of UTI or antibiotic usage may have a relatively low reliability. Second, we excluded patients who did not initially receive gentamicin, and cases that required urological interventions. These selection criteria may have biased the study by excluding more severe cases. Third, only 50 (18.2%) of 275 patients were microbiologically evaluable at the follow-up visit (4–10 days post-therapy). Fourth, ototoxicity was identified only if subjective symptoms of ototoxicity such as vertigo, tinnitus, dizziness or hearing impairment were found on the medical records.

In conclusion, gentamicin can be an efficient and economic antibiotic option for the initial empirical treatment of community-onset complicated APN, especially in patients who do not require urological procedures. The use of gentamicin may spare the use of fluoroquinolones or broad-spectrum cephalosporins in the treatment of complicated non-obstructive APN.

Transparency Declaration

The authors declare no conflicts of interest.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Kaplan–Meier survival plots of time to fever clearance.

Table S1. Factors associated with early clinical failure of women with community-onset complicated non-obstructive acute pyelonephritis due to Enterobacteriaceae.

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